

University of Groningen

On perinatal pathology

Gordijn, Sanne Jehanne

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gordijn, S. J. (2009). *On perinatal pathology: aspects of perinatal autopsy, placental pathology and classification of perinatal mortality*. [Thesis fully internal (DIV), University of Groningen]. [s.n.].

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CHAPTER 11

SUMMARY



With this thesis we provide clues that can help to understand the value of the perinatal autopsy and placental examination, the importance of good communication between pathologists and clinicians and the use of classification systems in perinatal mortality. The first chapters focus at the perinatal autopsy, the next chapters focus at placental investigation and the communication between the pathologist and clinician and the last at classification of perinatal mortality.

Chapter 2: Value of the perinatal autopsy: critique

This chapter illustrates the value of the perinatal autopsy. In this literature review the autopsy reveals new diagnoses or important additional information in 22% to 76% of cases. If confirmation of clinical findings is included, then the value of perinatal autopsy is as high as 100%. Several confounding factors that may influence the value of the autopsy have been evaluated including the level of hospital, the autopsy protocols used, the expertise of the pathologist (perinatal/pediatric pathologist, fellow or general pathologist) and also selection of cases admitted for autopsy. The autopsy protocols and expertise of the performing pathologists differed between the institutions. In several articles the autopsy protocol was unknown and the expertise of the pathologist remained indistinct. The autopsy rates varied between 16% and 100%, the mean autopsy rate was 38%. The highest rates were seen among terminations of pregnancy (79-100%).

The reported value of the autopsy can be positively influenced by selecting cases for admission to pathology in scenarios where the autopsy adds more information, for example by requesting more autopsies in the group of deaths with an unknown clinical diagnosis. Another possibility to improve the reported value of the autopsy is to exclude cases in which the autopsy cannot provide much information, for example in macerated stillbirth. In the published literature however the description of such selections of cases for autopsy is often not included, obscuring the possibilities for comparison of the value of perinatal autopsies.

Chapter 3: The perinatal autopsy: pertinent issues in multicultural Western Europe

This chapter deals with the difficulties that exist regarding counseling of the perinatal autopsy. The average autopsy rate is only 38%, which is less than the proposed minimum of 75% by the Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists. The major reason for the low perinatal autopsy rates is the difficulty of obtaining permission for the autopsy from the parents. Furthermore, the

assumption that the autopsy can be replaced by current imaging techniques, adverse publicity regarding organ retention (e.g. Alder Hey scandal) and reports on the failing quality of perinatal autopsies all contribute to the low autopsy rates. Parents should be informed about the routine of the autopsy. In general this involves macroscopic examination of the body and internal organs. Organs will be taken out for weighing and tissue will be sampled for histologic examination. The organs will be replaced, but the tissue samples not. These samples will be stored for additional analysis or second opinion.

Alternatives such as limited autopsy or needle biopsy of selected organs and imaging techniques such as MRI and radiography are available. These alternatives however are less conclusive than the "Gold Standard" i.e. the autopsy.

The major religions and their end-of-life rituals in general allow the performance of an autopsy. Some require special treatment or timing. In Buddhism for example the body has to be left undisturbed for three days to allow the soul to make its transition. In the Islam faith the autopsy should be performed as soon as possible as burial should take place before sunset of the next day. When doctors are convinced of the value of the autopsy and the parents are counseled adequately in respect of their cultural and religious background, the autopsy rates can be raised again.

Chapter 4: Quality of placental reports

In this chapter we investigate the quality of placental reports. Of 218 placental reports from four hospitals, two percent failed to reach half the maximum granted points (points were rewarded for description of, and commentary on, gross and histologic examination, comments on the associated clinical lesions and the availability of recurrence risks) and 31% scored between 50 and 75% of maximum granted points.

Several details of the placental reports attracted attention. In our analysis only 10% of reports stated the trimmed placental weight although the standard placental weight charts are based on trimmed weights. Some components of a placental report were well documented, such as the number of umbilical vessels, cord diameter and length and the dimensions of the placental discs. Other components were poorly documented such as completeness of membranes and location of membrane rupture. In almost all reports a block code for the placental samples was assigned, which is important for retrieval of samples for additional analysis or for a second opinion. Commentary on the findings of the placenta and the possible relation to clinical details differed between the hospitals and ranged between 43% and 94%.

The description of normal findings is of equal importance as the description of abnormal findings, otherwise it remains unknown whether details have been studied if not mentioned at all. Communication between pathologist and clinician is lost by inconsistent reporting of commentaries on (ab)normal findings in the placental reports.

Chapter 5: Histopathological examination of the placenta: key issues for pathologists and obstetricians

In this chapter we illustrate the importance of placental examination and the importance of good communication about the results between the clinician and the pathologist. The placenta is often not submitted for histopathological examination, as clinicians are often sceptical as to the value of placental examination.

When a placenta is submitted to the pathologist, adequate details considering conditions in pregnancy and medical history for the interpretation of placental findings should be provided. The request form for placental investigation should therefore contain a list with important information for the pathologist (preferably a standardized form). In return, the obstetrician should be provided with adequate information for interpretation of the histological findings and the subsequent counseling of the parents.

Chronic villitis (lymphohistiocytic inflammation of the terminal villi) is an example of a histological diagnosis. It has an unknown aetiology and is associated with intrauterine growth restriction, preterm labour and fetal death, with a recurrence risk of up to 17%. In future pregnancies the foetus can be monitored by ultrasound and cardiotocography. Acute chorioamnionitis (associated with pathogenic vaginal microorganisms) is another example with a recurrence risk and possibilities for intervention.

For explanation and interpretation of histological abnormalities the involvement of pathologists in multidisciplinary meetings with obstetricians and neonatologists can be very useful, particularly in the case of apparent unexplained stillbirth or serious adverse outcome.

Chapter 6: Villous immaturity as an important cause of term foetal death

Villous immaturity of the placenta is an important cause of death in term intrauterine foetal deaths (over 252 days or 36 weeks of gestation). We evaluated 1025 foetal deaths and selected the cases beyond 36 weeks of gestation ($n = 352$). Based on the causes of death the intrauterine foetal deaths were divided in three groups: villous immaturity, other placental pathology and non-placental pathology.

A placental cause of death was identified in almost 80% (280/352). Of the placental causes 29% (81/280) were caused by villous immaturity. Of these cases 48% were caused by villous immaturity alone and 52% by villous immaturity in combination with other placental pathology. The prevalence of gestational diabetes was 2.5 fold-higher in the villous immaturity group than in the group caused by other placental pathology (13.9% vs. 5.5%) ($p = 0.029$) and 10 fold- higher than in the group caused by non-placental pathology (13.9% vs. 1.4%) ($p = 0.005$). Villous immaturity was also associated with placental hypoplasia in comparison to the group with a non-placental cause of death. Although oligohydramnios occurred almost twice as often in the group with villous immaturity (23.1%) than in the group with non-placental causes (12.5%), was this difference not statistically significant ($p = 0.139$). No associations were found for pre existent diabetes mellitus, hypertensive disorders, intoxications or foetal characteristics such as foetal weight. Previously described association with hyper coiling of the umbilical cord could not be confirmed.

Chapter 7: The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement

We developed a perinatal mortality classification system for cause and mechanism of death. The Tulip classification system classifies the underlying cause of death, defined as the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death, in 6 categories; 1: congenital anomalies, 2: placenta, 3: prematurity/immaturity, 4: infection, 5: other and 6: unknown. These main categories contain several subcategories. The system consequently classifies the mechanism of death (defined as the organ failure incompatible with life) and the origin of the mechanism. Finally, contributing factors (conditions like hypertension preeclampsia or risk factors such as smoking) are classified. We provide clear definitions and guidelines for case allocation.

After development of the system it has been tested for the inter-rater agreement between five panel members in 411 cases of perinatal mortality. The largest cause of death group was: congenital anomalies (35%), the second and third largest groups were placental and prematurity (27% and 23% respectively). Only 11% of deaths were allocated to the "unknown" group. The infection and "other" categories consisted of only 1% and 3% of deaths respectively. The kappa score was 0.81 for main cause of death (0.89 after excluding guideline misinterpretations) and 0.67 for sub classification of cause of death (0.76 after excluding guideline misinterpretations). The agreement

was highest in the congenital anomalies category and lowest in the category “other”. To clarify some classification difficulties examples of cases have been provided.

Chapter 8: A Placental cause of intra-uterine foetal death depends on the perinatal mortality classification system used

Differences between perinatal mortality classification systems have consequences for vital statistics. We illustrated this by classification of 485 cases of foetal death in eight perinatal mortality classification systems (extended Wigglesworth, modified Aberdeen, ReCoDe, Tulip, and the classifications by Hey et al., Hovatta et al., de Galan-Roosen et al. and Morisson et al.). The cases were classified in a panel with two obstetricians, a pathologist and a registrar in Obstetrics and Gynaecology. Distribution of the 485 stillbirth cases into the different causal categories varied among the systems, predominantly in the “placental” and the “unknown” groups. The proportion of cases (for the same 485 cases) in the placental groups varied from 0% (no placental category provided in those systems) to 64.3% in the Tulip classification. In some systems cases with an unexplained cause of death comprised the largest group such as in the extended Wigglesworth (88.5%), while in other systems such as the system by Hey et al. no deaths were classified as unexplained. However in this system 88.4% of cases were allocated to the group “asphyxia antepartum”.

Systems that lack a placental category and systems that allocate most cases to the “unknown” categories or to categories that comprise only clinical manifestations are not discriminatory for the underlying cause of death. Allocation of cases according to the underlying cause of death resulted in the largest group of deaths in the placental category and the most frequent contributing factor was intrauterine growth restriction.

Chapter 9: A multidimensional approach for the analysis of perinatal mortality using different classification systems

We identified 35 classification systems for perinatal mortality published since 1954. All systems have their own strengths and weaknesses, but none of them has been universally accepted for its use. In this chapter we propose a multilayered approach that uses the existing systems based on information related to the moment of death, the conditions associated with death and the underlying cause of death. Three questions in sequence of complexity can be asked: *When did it happen?* What was the gestational age and when did it occur? Antepartum, intrapartum or in the neonatal period? Two systems mainly focus at when death occurred. They both include a category for lethal

foetal malformations as well. For reliable allocation of cases foetal macroscopy is required. The next question that can be asked is: *What happened?* What were the fetal, maternal and/or placental conditions that have contributed to death? To answer this question more investigations are necessary: analysis of clinical conditions, foetal and placental macroscopy and preferably the autopsy as well. Most of the developed systems classify what happened. The final and most complex question that can be asked is: *Why did it happen?* What is the underlying cause of death, the event that initiated the chain of events that eventually resulted in death? Extensive analysis including placental histopathology is required to reliably allocate the cases to these categories.

Classification systems that do not have adequate placental categories or have categories such as hypoxia or antepartum haemorrhage are not considered to classify the underlying cause of death. When causes and conditions are mixed within a system, overlap in allocation is possible. Information is then lost and comparison is unreliable. When cause and condition are used separately, they add to each other, which is why we propose the multilayered approach.

For audit purposes cross tables of the different systems can be made to see the relation between timing of death, conditions, underlying cause and additionally possible substandard factors in the care.

